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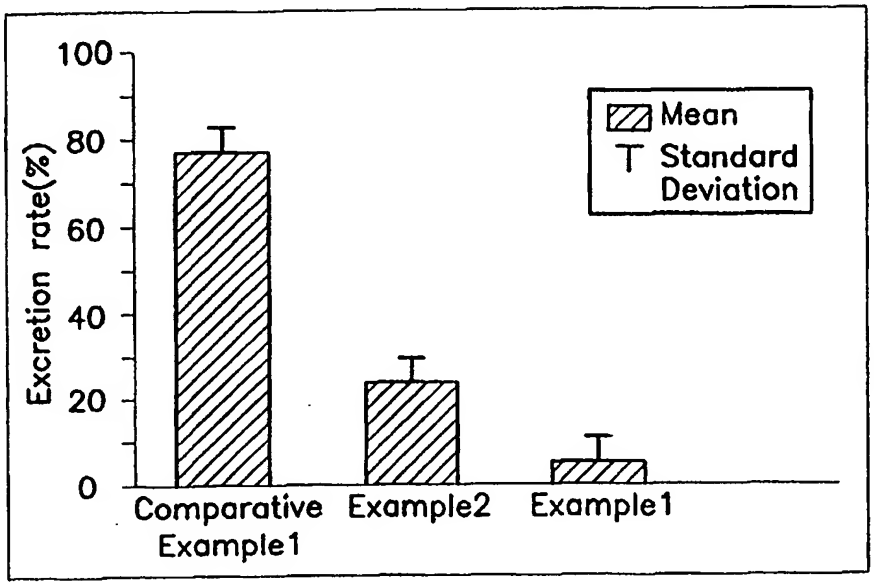

(57) Abstract

A method of preparing a pharmaceutical active ingredient comprising a water-insoluble drug is provided. In the method, a water-insoluble drug in an organic solvent is mixed with a water-soluble polymer in an aqueous solvent and spray-dried. Thereafter, the drug microparticles is mixed with oil. The method can easily prepare a pharmaceutical active ingredient including water-insoluble drug, exhibiting good bioavailability. Accordingly, it is not required for specific technology in the preparation.

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METHOD OF PREPARING PHARMACEUTICAL ACTIVE INGREDIENT COMPRISING WATER-INSOLUBLE DRUG AND PHARMACEUTICAL COMPOSITION FOR ORAL ADMINISTRATION COMPRISING THE SAME

BACKGROUND OF THE INVENTION

(a) Field of the Invention

The present invention relates to method of preparing a pharmaceutical active ingredient comprising water-insoluble drug and a pharmaceutical composition for oral administration comprising the same and, more particularly, to a method of preparing a pharmaceutical active ingredient comprising the water-insoluble improved bioavailability with simple process.

(b) Description of the Related Art

When a water-insoluble drug is orally administrated into a patient, bioavailability is low. Due to the low bioavailability, it is impossible to orally administrate the water-insoluble drug or for increasing the effective concentration of the drug in the blood, the patient frequently takes the water-insoluble drug for a long time. For example, the patient takes the water-insoluble drug three times a day for a week.

For improving bioavailability, studies to use oil and a surfactant has been attracted. Korean Patent Laid-open No. 96-21056 discloses that a drug is micro-emulsified by using oil and a surfactant. Furthermore, a drug is dissolved in an organic solvent and the mixture is micro-emulsified by using oil and a surfactant (Sandoz company, Swiss).

In addition, Korean Patent Laid-open No. 96-5136 discloses that drug in

alcohol such as ethanol or isopopanol or acetone is mixed with excess water under the condition of forming hydrosol and dried by rotary drying or freeze-drying to make preparation.

However, in the methods of Korean Patent Laid-open No. 96-21056 and Sandoz company, the surfactant used hurts gastrointestinal tract. Furthermore, the method of Korean Patent Publication No. 96-5136 has disadvantages in that manufacturing process is complicate and it is required specific manufacturing technology.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method of preparing a pharmaceutical active ingredient comprising a water-insoluble drug with simple and economical process.

It is another object of the present invention to provide a pharmaceutical composition for oral administration comprising the water-insoluble drug.

These and other objects may be achieved by a method of preparing a pharmaceutical active ingredient comprising a water-insoluble drug. The method includes the steps of mixing a water-insoluble drug in an organic solvent with a water-soluble polymer in an aqueous solvent and spray-drying the mixture.

Furthermore, the present invention provides the pharmaceutical composition for oral administration including a pharmaceutical active ingredient including water-insoluble drug microparticles combined with a water-soluble polymer.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete appreciation of the invention, and many of the attendant advantages thereof, will be readily apparent as the same becomes better understood by reference to the following detailed description when considered in conjunction with the accompanying drawing, wherein:

FIG. 1 is a graph showing water-insoluble drug excretion rate after pharmaceutical compositions including pharmaceutical active ingredients of examples 1 to 2 and comparative example 1 is oral administrated; and

FIG. 2 is a schematic diagram showing sprayer for producing water-insoluble drug microparticles combined with a water-soluble polymer used in the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical active ingredient including water-insoluble drug. The pharmaceutical active ingredient exhibits good bioavailability. For that purpose, in the present invention, microparticles is formed by using a water-insoluble drug and water-soluble polymer without a surfactant which causes gastrointestinal tract damage.

The method of preparing pharmaceutical product for oral administrating water-insoluble drug will be described in more detail.

A water-insoluble drug is dissolved in an organic solvent such as acetone to prepare a drug solution. As the water-insoluble drug, ipriflavone, biphenyl dimethyl dicarboxylate and cyclosporin may be used.

A water-soluble polymer is dissolved in an organic solvent such as

ethanol aqueous solution to prepare a polymer solution. As the water-soluble polymer, cellulose type compound may be used. The exemplary of cellulose type compound is ethylcellulose, polyethyleneglycol, carboxymethylcellulose, polyethyleneglycol, polyvinylpyrollidone, dextran, poloxamer and a mixture thereof.

The drug is mixed with the polymer in the weight ratio of 1 : 0.1 to 10, preferably 1 : 0.1 to 2. The mixed solution is spray-dried, thereby obtaining water-insoluble drug powder, microparticles combined with water-soluble polymer.

For obtaining microparticles, since rotary-evaporation or freeze-dry step has been used in the conventional process, the preparation is complicate, thereby requiring the specific technology. On the contrary, in the present invention, according to the performance of the spray-drying step, the preparation is simple and therefor, it is not required the specific technology. The exemplary of a spray dryer used in the spray-drying step in the present invention is shown in Fig. 2. As shown in Fig.2, the mixed solution and air are injected into a spray-dryer body, while raising the ambient temperature by the heated air and mixed solution is changed from solution form to microparticle form by heated air.

For increasing bioavailability, the drug microparticles combined with polymer may be mixed with oil in the weight of 1 : 1 to 10. It is preferred that the drug microparticles mixed with oil because bioavailability increases. When oil amount is lower than 1, it is difficult to mix the drug micropartices with oil. On the contrary, oil amount exceeds 10, it is difficult to charge the mixture to a

capsule. As the oil, corn oil, peanut oil, coconut oil, caster oil, sesame oil, perilla oil, sunflower oil, walnut oil and cacao butter may be used.

The water-insoluble drug microparticles combined with water-soluble polymer may be used as an active ingredient for a pharmaceutical composition for oral administration.

The pharmaceutical composition further includes vehicle or a disintegrant, a lubricant. In addition, the pharmaceutical compositon may inlcude other pharmaceutical excipients such as stabilizer, a preservatives, an electrolyte, etc used in the pharmaceutics

The present invention is further explained in more details with reference to the following examples. The examples are not intended to limit the present invention.

Example 1

1 part by weight of ipriflavone was dissolved in 8 parts by weight of acetone to prepare a water-insoluble drug solution. 2 parts by weight of hydroxypropylmethylcellurose was dissolved in an aqueous ethanol solution including 1 part by weight of water and 1 part by weight of ethanol to prepare a water-soluble polymer solution. 4 parts by weight of the polymer solution was added to 9 parts by weight of the drug solution and mixed well by using a homogenizer. The mixed solution was spray-dried at 50 ℃ for 20 minutes by using a spray-dryer shown in Fig.2 to obtain the water-insoluble drug microparticles combined with water-soluble polymer. 3 parts by weight of the drug microparticles was mixed with 10 parts by weight of corn oil to obtain a pharmaceutical active ingredient.

Example 2

A pharmaceutical active ingredient was prepared by the same procedure in Example 1 except that corn oil was not used.

Comparative example 1

The commercial product of Ipriflavone was used for oral administrating water-insoluble drug.

Pharmaceutical compositions of the present invention were prepared by the conventional pharmaceutical process with these pharmaceutical active ingredients of examples 1 to 2. Furthermore, pharmaceutical compositions of comparative example 1 was prepared by disintegrating 0.27 parts by weight of Ipriflavone of comparative example 1 in water. These pharmaceutical compositions was used as powder or tablets. These tablets or powder were oral administered into white rats in the amount of 50 mg of drug per kg of rat's weight with conventional method. The amounts of ipriflavone in the tablets or powder which did not absorbed in the rat's body and excreted to the out of the body were determined. The result shows in Fig. 1.

The result of comparative example 1 show that the most of ingredient ipriflavone did not absorbed in the rat's body and excreted to the out of the body were shown in Fig. 1. As shown in Fig. 1, when the pharmaceutical active ingredient including the drug microparticles and water of the Example 2 was oral administered, absorption in the body increased two times more than the Comparative example 1. Furthermore, when the pharmaceutical active ingredient including oil of example 1, absorbing in the body is seven times more than the comparative example 1.

As described above, when the drug microparticles obtained by the present invention is oral administered with oil, the increased bioavailability is exhibited. Accordingly, the drug of the present invention can be oral administered. Furthermore, it is not required for the drug to administered into a patient three or four times a day rather than the conventional water-insoluble drug.

While the present invention has been described in detail with reference to the preferred embodiments, those skilled in the art will appreciate that various modifications and substitutions can be made thereto without departing from the spirit and scope of the present invention as set forth in the appended claims.

WHAT IS CLAIMED IS:

1. A method of preparing a pharmaceutical active ingredient composition including water-insoluble drug for oral administration comprising the steps of:

mixing water-insoluble drug in an organic solvent with water-soluble polymer in an aqueous solvent;

spray-drying the mixture.

2. The method of claim 1 wherein the polymer is selected from the group consisting of ethylcellulose, polyvinylpyrrolidone, polyethyleneglycol, carboxymethylcellulose, hydroxypropylmethylcellurose, dextran and poloxamer.

3. The method of claim 1 wherein the drug is selected from the group consisting of ipriflavone, biphenyldimethyldicarboxylate and cyclosporin.

4. The method of claim 1 wherein the weight ratio of the drug and polymer is 1 : 0.1 to 10.

5. The method of claim 1 further comprising the step of mixing the microparticles with oil.

6. The method of claim 1 wherein the oil is selected from the group consisting of corn oil, peanut oil, coconut oil, castor oil, sesame oil, perilla oil, sunflower oil, walnut oil and cacao butter.

7. The method of claim 5 wherein the weight ratio of the microparticles and oil is 1 : 1 to 10.

8. A pharmaceutical composition for oral administration, comprising a pharmaceutical active ingredient water-insoluble drug microparticles combined with water-soluble polymer.

9. The pharmaceutical composition of claim 8 wherein the drug is selected from the group consisting of ipriflavone, biphenyldimethyldicarboxylate and cyclosporin.

10. The pharmaceutical composition of claim 8 wherein the polymer is selected from the group consisiting of ethylcellulose, polyvinylpyrrolidone, polyethyleneglycol, carboxymethylcellulose, hydroxypropylmethylcellurose, dextran and poloxomer.

FIG.1

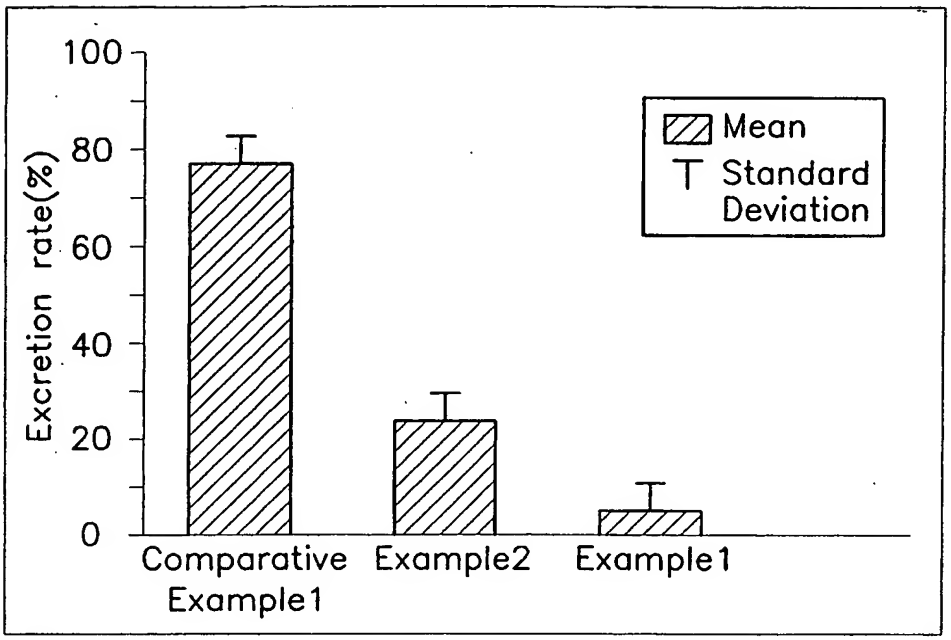
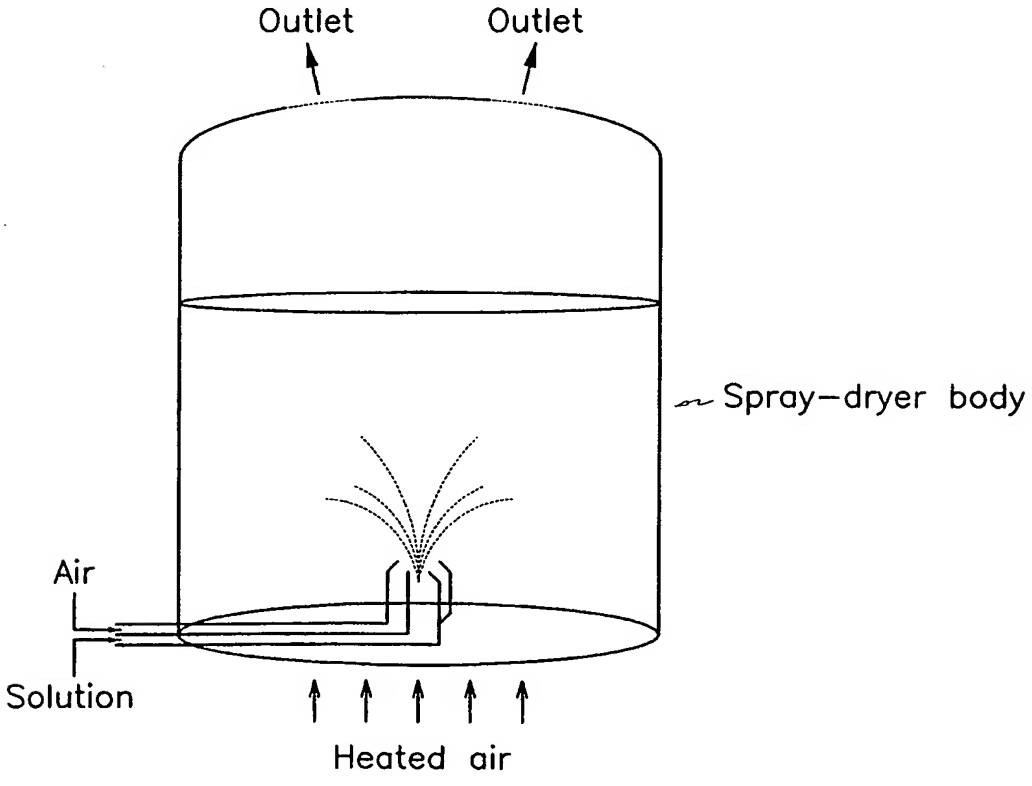

100
80
60
40
20
0
Excretion rate(%)
Mean
Standard Deviation
Comparative Example1
Example2
Example1

FIG.2


Outlet
Outlet
Spray-dryer body
Air
Solution
Heated air

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00025

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A 61 K 9/14, A 61 K 47/44, A 61 K 38/13, A 61 K 47/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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WPI, TXTE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 012 496 A1 (BEECHAM GROUP LIMITED) 25 June 1980 (26.06.80), abstract; page 3, lines 1-16; page 4, lines 18-21; page 5, lines 1-12.	1,2,4,8

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Date of the actual completion of the international search	Date of mailing of the international search report
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